Article published online: 2022-07-14

Case Report

Nephrocalcinosis in Genetically Proved DOPA-Responsive Dystonia Due to Sepiapterin Reductase Deficiency in a Libyan Girl

Samira A. Etarhuni[1], Adel M. Zeglam[1], Awatef S. Elbouaishi[2], Abdulbast Mahdi Sharfddin[3]

Departments of [1]Pediatric Neurology, [2]Pediatric Nephrology and [3]Radiology, Tripoli University Hospital, Tripoli, Libya

Abstract

Dopa-responsive dystonia (DRD) encompasses clinically and genetically heterogeneous disorders that typically manifest as limb-onset, diurnally fluctuating dystonia and exhibit a robust and sustained response levodopa treatment. GCH1 gene mutations are the most frequent cause of DRD. Mutations in the TH or SPR gene less often cause this condition. The index case is a 12-year-old young girl presented to the pediatric neurology clinic at the age of 8 years with tiptoes walking and deterioration of her gait. She is the product of first-degree consanguineous marriage with insignificant history. The index case has two sisters, one of whom suffers from learning difficulties, epilepsy, and bilateral nephrocalcinosis. Her two uncles had severe axonal polyneuropathy and died in their forties of unknown cause. Her magnetic resonance imaging of the brain demonstrated agenesis of the corpus callosum. Renal ultrasound studies showed bilateral nephrocalcinosis. Genetic DNA evaluation (whole-exome sequencing) identified the heterozygous variant c.207C>G,p. (Asp69Glu) in the SPR gene (OMIM: 182125), which leads to an amino acid exchange. Nine out of ten bioinformatic in silica programs predict a pathogenic effect for this variant. Treatment with levodopa\ benserazide 4:1 (Madopar) has not made any changes to the girl's condition.

Keywords: Dopa-responsive dystonia, Libya, nephrocalcinosis, sepiapterin reductase

Introduction

Dystonia is a movement disorder characterized by persistent and intermittent muscle contractions that cause involuntary repetitive movements, leading to abnormal posture in affected parts of the body.[1] Hermann Oppenheim (1858–1919) described the first case of dystonia in 1911. In1994, the mutation in the GTP cyclohydrolase1 gene was discovered as a leading cause of DRD.[2]

DRD constitutes a group of clinically and genetically different movement disorders that

Access this article online

Quick Response Code:

Website: www.ijmbs.org

DOI: 10.4103/ijmbs.ijmbs_53_20

Address for correspondence: Dr. Samira A. Etarhuni, Department of Pediatric Neurology, Tripoli University Hospital, Tripoli, Libya. E-mail: samiraracd@yahoo.com

Submitted: 09-May-2020 **Revised:** 15-Aug-2020
Accepted: 18-Aug-2020 **Published:** 04-Nov-2020

How to cite this article: Etarhuni SA, Zeglam AM, Elbouaishi AS, Sharfddin AM. Nephrocalcinosis in genetically proved dopa-responsive dystonia due to sepiapterin reductase deficiency in a Libyan Girl. Ibnosina J Med Biomed Sci 2020;12:315-9.

typically manifest by dystonia of limbs with diurnal fluctuation and exhibit a clear and continuous response to levodopa drugs.[3] DRD is caused by three different genes – GCH1, TH, and SPR. The most common are the mutations in the GCH1 gene, followed by mutations in the TH and SPR genes.[4,5]

The GCH1 gene regulates the synthesis of the GTP cyclohydrolase enzyme, responsible for the first three steps in the production of tetrahydrobiopterin (BH4) molecule. The SPR gene controls for the synthesis of the sepiapterin reductase enzyme, which is involved in the last step of BH4 production.[4] The classical forms of BH4 deficiency manifest by hyperphenylalaninemia, while DRD and SPR deficiency are not, and hence the neonatal screening for phenylketonuria (PKU) cannot detect it.[6]

DRD, due to (SPR) deficiency (OMIM#612716), is a rare genetic movement disorder caused mainly by an autosomal recessive[5] and rarely by dominant mutations.[7] The clinical manifestations of SPR deficiency range from a mild movement disorder at one end to a severe progressive neurological disease at the other end.[5] The SPR enzyme converts a molecule called 6-pyruvoyl-tetrahydropterin to tetrahydrobiopterin molecule. Tetrahydrobiopterin is involved in neurotransmitters' production; the neurotransmitters carry signals between nerve cells in the brain. Most notably, tetrahydrobiopterin is involved in the production of two neurotransmitters called dopamine and serotonin. Among their many functions, dopamine transmits signals within the brain to smooth physical movements, and serotonin is responsible for regulating emotion, mood, appetite, and sleep.[4] The majority of affected individuals' clinical features include motor and speech delay, axial hypotonia, dystonia, weakness, and oculogyric crises; symptoms usually show diurnal fluctuation. Other standard features include parkinsonian signs (tremor, rigidity, masked face, and bradykinesia), limb hyperreflexia, hypertonia, autonomic dysfunction, intellectual disability, psychiatric and/or behavioral abnormalities, and sleep disturbance (excessive sleep, difficulty initiating, or maintaining sleep). The disease features are nonspecific in the first year of life, which includes developmental delays and axial hypotonia; other features develop over time.[5]

Here, we report a new heterozygous variant c.207C>G,p. (Asp69Glu) in the SPR gene (OMIM: 182125), which leads to an amino acid exchange. Nine out of ten bioinformatic *in silico* programs predict a pathogenic effect for this variant.

Case Report

History

A 12-year-old girl presented at the age of 8 years with tiptoes walking and deteriorated gait. She has no diurnal variation of her symptoms. She is a product of first-degree consanguineous marriage with insignificant history. She has two sisters; the younger one has global developmental delay, epilepsy, and bilateral nephrocalcinosis. Her two uncles had severe axonal polyneuropathy and died in their forties of unknown cause. This family is an Arab family from Libya. On examination, she had high-stepped and broad-based gait. She was alert with normal higher mental function. She had mask face, normal cranial nerves, normal head size, and average body built. Her muscle tone was increased, and her tendon reflexes were exaggerated. She had sustained clonus. Her muscle power was grade 5. Her systemic examination was unremarkable.

Investigations

The patient's initial workup was unremarkable. Her abdominal and renal ultrasound showed bilateral nephrocalcinosis; complete investigations were done to find the cause of here nephrocalcinosis, were all normal including serum calcium level, phosphorus, alkaline phosphatase, parathyroid hormone, Vitamin D level, arterial blood gases, serum sodium and potassium, blood urea, and creatinine. In addition, she had a normal urinary anion gap, normal urine routine examination, and normal 24-h collection for calcium to creatinine ratio. Hence, a diagnosis of idiopathic nephrocalcinosis was most likely. Brain MRI showed periventricular leukomalacia with right frontal subcortical lacunar gliosis [Figure 1]. Genetic

DNA evaluation (whole-exome sequencing [WES]) identified the heterozygous variant c.207C>G,p.(Asp69Glu) in the SPR gene (OMIM: 182125), which leads to an amino acid exchange. Nine out of ten bioinformatic *in silico* programs predict a pathogenic effect for this variant [Figure 2].

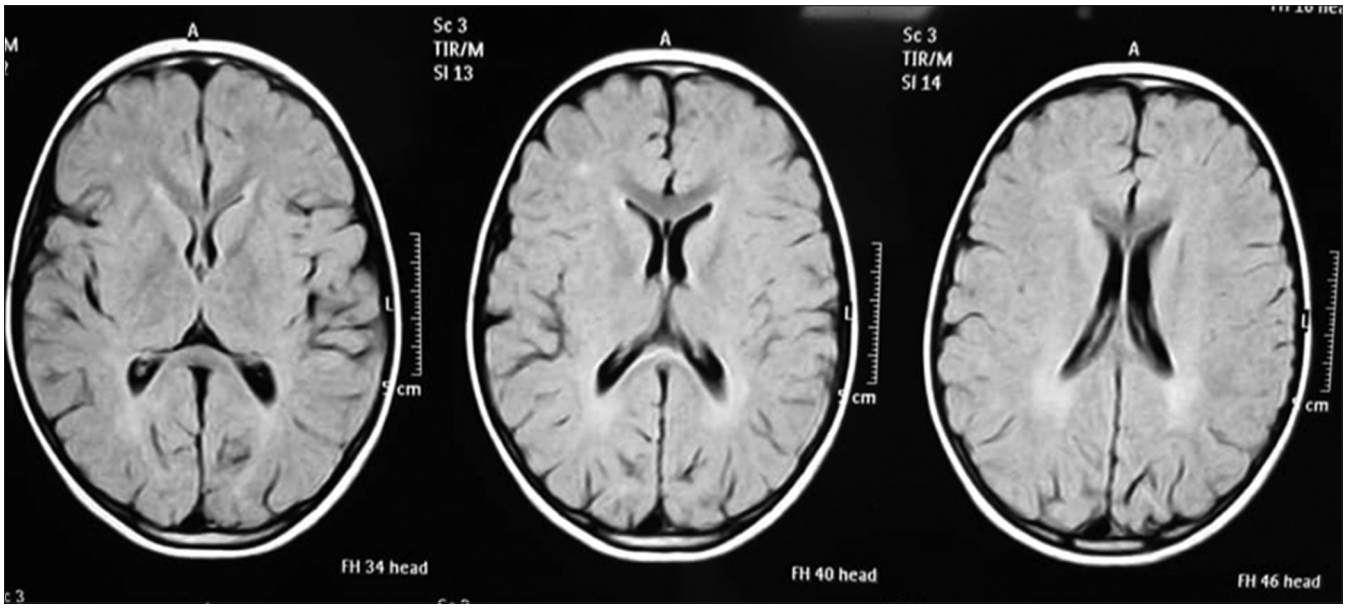

Figure 1: Magnetic resonance imaging brain performed using a dedicated head coil on a 1.5 tesla scanner, the fluid-attenuated inversion recovery images revealed bilateral cerebral hemisphere periventricular deep white matter high signal intensity going with periventricular leukomalacia with right frontal subcortical lacunar gliosis

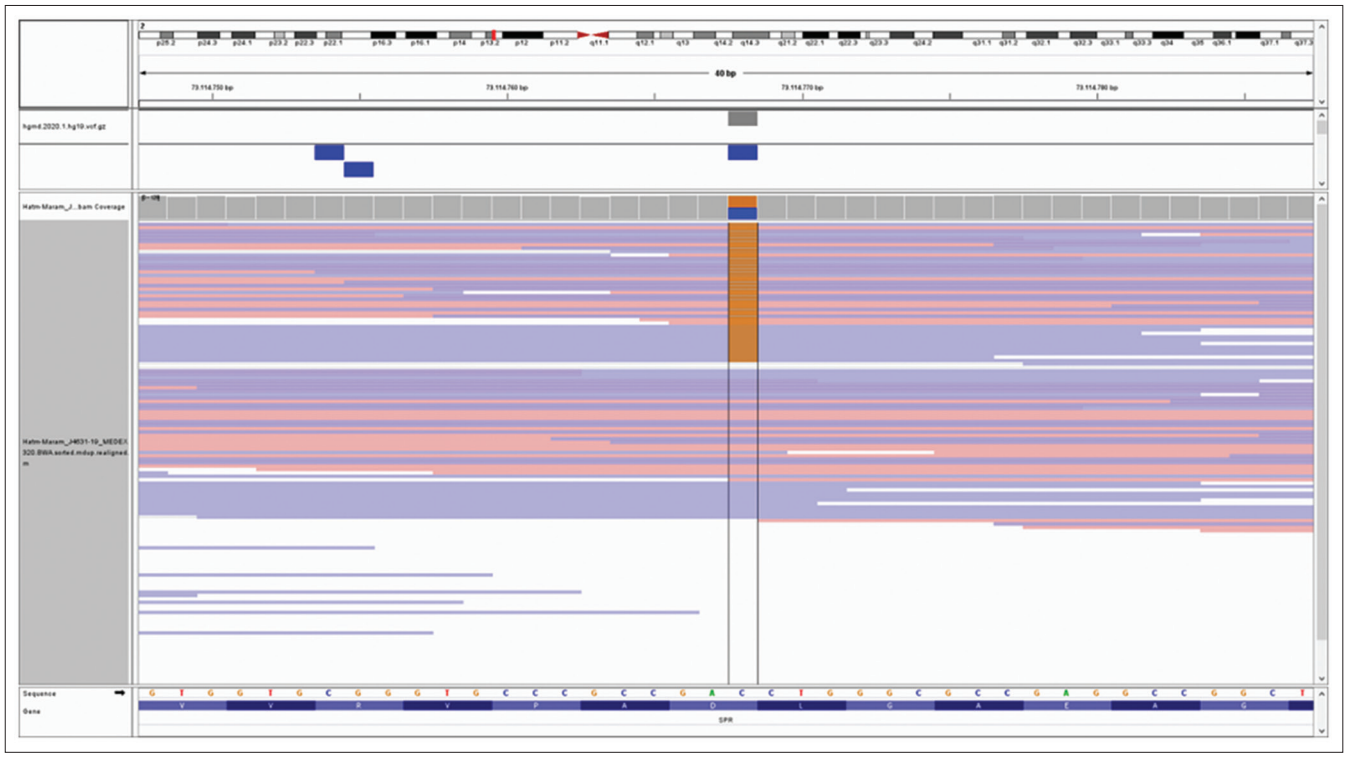

Figure 2: An alignment view of the variant gene SPR leading to a frameshift mutation indicted by a vertical shadow line (cytogenetic location: 2p13.2, which is the short [P] arm of chromosome 2 at position 13.2)

Discussion

To the best of our knowledge, the association of this variant with nephrocalcinosis has not been described previously. However, a similar variant has already been described in the literature in a family with autosomal dominant DRD with incomplete penetrance (PMID: 29147684). The variant is found in 0.01% of the overall population (12 heterozygous, 0 homozygous; gnomAD), and this is the first time the variant was detected in the internal laboratory database. Considering the available information, the variant was classified as a variant of uncertain significance (Bioscientia International). Molecular genetic study for parents showed that the father carries c.207C>G,P.(Asp69Glu) in SPR in a heterozygous state, while the mother is not a carrier of the same gene.

More than 20,000 genes in the human genome were enriched using Roche/NimbleGen technology (SeqCap EZ MedExome Library) and sequenced on an illumine HiSeq 1500 system (WES). The aberrations listed were identified by filtering the exome data for homozygous/putatively compound–heterozygous variant, bioinformatically extracted homozygousity-by-descent regions and by a literature-based survey against the indication of interest.

DRD comprises a genetically heterogeneous group of movement disorders with both autosomal dominant and recessive traits,[4,8] The phenotypic spectrum of SPR deficiency has not been completely elucidated due to the small number of affected people. In 2015, a total of fifty cases were reported all over the world.[5] Focusing on the Middle Eastern and North Africa (MENA) region, ten more cases from Saudi Arabia and Egypt were reported in 2017.[7,9] Also another case was reported from Jordan in 2019.[9]

Comparing our case with those from the same MENA region may be of particular interest. Our patient carries a heterozygous SPR variant (c.207C.G,p.Asp69Glu, chr2:73114768_C.G.), a mutation has also been described in one Egyptian family.[7] Our patient's father carries the same gene, supporting the autosomal dominant inheritance with incomplete penetrance in this family.

Also, comparing our case with the five affected children in the Egyptian family[7], reveals a similarity in the age of onset with most of the cases seen between childhood and puberty. The clinical presentation of all cases was with lower limb dystonia (tiptoe walking) and rigidity that started early in childhood and had a progressive course. Regarding the response to treatment, the first patient in the Egyptian family has improved markedly with L-DOPA, however, with low-threshold drug-induced dyskinesia. His current medications include fractionated L-DOPA doses (750 mg/day), anticholinergic, and amantadine (400 mg/day). The second and third children experienced symptomatic benefit with L-DOPA and continued on pramipexole. Children 4 and 5 were not treated with L-DOPA because of their age, minor symptoms, and fear of L-DOPA-induced dyskinesia. Treatment of our patient with levodopa/benserazide 4:1 (Madopar) has not changed her condition. She has not shown any improvement in fractionated L-DOPA doses (750 mg/day) for a 6-month duration.

Nephrocalcinosis, which is seen in our case, has never been reported previously in any published cases of DRD due to the SPR deficiency, and its relation to the child's condition seems to be unclear. Further research is required to confirm the relationships and elucidate its mechanisms.

Conclusions

We suggest that the new variant (207C>G,p [Asp69Glu]) of the gene responsible for DRD due to SPR deficiency detected in our patient and the Egyptian patient is likely to be pathogenic rather than of uncertain significance. This is supported by the phenotypic and the genotypic similarities, both being inherited as autosomal dominant with incomplete penetrance. DRD due to SPR deficiency is infrequent, but the real number of cases may be underestimated due to a lack of diagnosis. WES is an essential tool for diagnoses, but it is costly, especially in the third world. The association of nephrocalcinosis and DRD is not clear, but further researches are needed.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given consent for the patient's

images and other clinical information to be reported in the journal. The guardian understands that the patient's name and initial will not be published, and due efforts will be made to conceal patient identity, but anonymity cannot be guaranteed.

Acknowledgment

The authors are grateful for the help and support of the patient's family.

Authors' contributions

All authors were involved in the clinical care of patients, undertaking the investigative studies and drafting and finalizing of the manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Compliance with ethical standards

No prior ethical approval is required for single case reports. However, the patient provided consent for publication as stated above.

References

1. Albanese A, Bhatia K, Bressman SB, Delong MR, Fahn S, Fung VS, *et al*. Phenomenology and classification of dystonia: A consensus update. Mov Disord 2013;28:863-73.
2. Klein C. Genetics in dystonia. Parkinsonism Relat Disord 2014;20 Suppl 1:S137-42.
3. Wijemanne S, Jankovic J. Dopa-responsive dystonia--clinical and genetic heterogeneity. Nat Rev Neurol 2015;11:414-24.
4. Asmus F, Gasser T. Dystonia-plus syndromes. Eur J Neurol 2010;17 Suppl 1:37-45.
5. Friedman J. Sepiapterin reductase deficiency. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, *et al*., editors. GeneReviews®. Seattle (WA): University of Washington, Seattle; 1993-2020.
6. Blau N, Bonafé L, Thöny B. Tetrahydrobiopterin deficiencies without hyperphenylalaninemia: Diagnosis and genetics of dopa-responsive dystonia and sepiapterin reductase deficiency. Mol Genet Metab 2001;74:172-85.
7. Shalash AS, Rösler TW, Müller SH, Salama M, Deuschl G, Müller U, *et al*. c.207C>G mutation in sepiapterin reductase causes autosomal dominant dopa-responsive dystonia. Neurol Genet 2017;3:e197.
8. Froukh T. Genetic study in a family with dopa-responsive dystonia revealed a novel mutation in sepiapterin reductase gene. Pak J Med Sci 2019;35:1736-9.
9. AlSubhi S, AlShahwan S, AlMuhaizae M, AlZaidan H, Tabarki B. Sepiapterin reductase deficiency: Report of 5 new cases. Eur J Paediatr Neurol 2017;21:583-6.